FACTORS AFFECTING THE OUTCOMES OF SEPSIS

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TOPICS TO BE DISCUSSED

1. Perspective on human sepsis.

2. Clinical evidence that exposure to radiation (and chemotherapy) increases the incidence of sepsis in humans.

3. Experimental models of sepsis and mediators involved.

HUMAN SEPSIS - A PERSPECTIVE

1. Affects ~600,000 individuals in North America per year.

2. Mortality rate varies from 30-60%.

3. Estimated costs for patient care -$18 billion/yr.

4. Except for activated protein C, therapy is supportive in nature (ventilator support, vasopressors, etc.)

SOURCES OF HUMAN SEPSIS*

A. Infectious Agents:

Gram+ bacteria: 52% (increasing incidence of MRSA)
Gram- bacteria: 37%
Polymicrobial: 5%
Fungal: 5%
Anaerobic bacteria: 1%

B. Sites:

Lung: 42%
Genitourinary: 13%
Intraabdominal: 12%

C. Issue of MRSA

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* *Carrigan, et.al., Clinical Chemistry, 2004, 50:1301-1314.*

MECHANISMS FOR IONIZING RADIATION INCREASING INCIDENCE OF LETHAL SEPSIS

1. **Bone marrow and lymphoid suppression.**

2. **Thoracic radiation induces ARDS and a 5-fold increase in post-operative sepsis.**

   Reynolds, et.al., J. Thor. Surg. 2006, 132:549-555.

3. **Abdominal radiation reduces GI content of aerobic and anaerobic bacteria, resulting in greatly increased numbers of *Enterobacteriaceae*, a cause of lethal sepsis.**

   Brooks, et.al., Disaster Med. 1993, 8:85-88.
   and Mil. Med. 2004, 169:194-197.

EXPERIMENTAL MODELS OF SEPSIS

1. Intravenous infusion of live *E. coli*.
2. Endotoxemia
3. Cecal ligation and puncture (CLP)
4. Ascending colonic stent
5. Intraperitoneal placement of fecal pellets
6. Bacterial pneumonia

MEDIATORS OF EXPERIMENTAL SEPSIS

1. Cytokines / Chemokines
2. MIF
3. HMGB-1
4. C5a and C5a receptors (C5aR and C5L2)
5. Others

POTENTIATION OF SEPSIS LETHALITY BY A "SECOND HIT"*

CLP followed by bacterial pneumonia *(Psuedomonas a.; Streptococcus p.)* results in:

a. **Greatly increased apoptosis of lymphocytes**

b. **Reduced serum levels of pro-inflammatory cytokines and chemokines**

c. **Greatly increased rate of lethality**

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* *Muenzer, et.al., SHOCK, 2006, 36:565-570.*

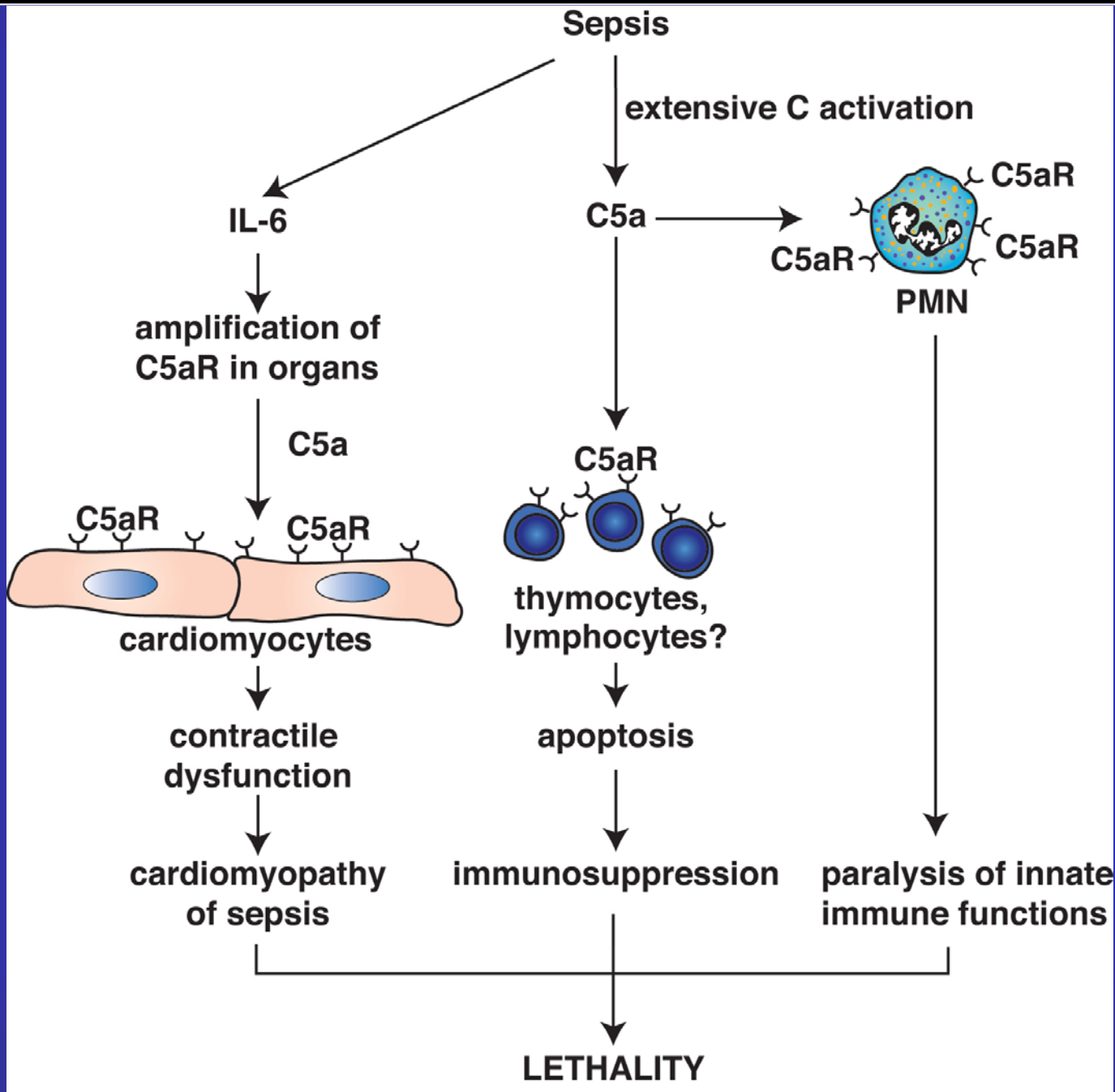
EVIDENCE FOR HARMFUL EFFECTS OF PMNs IN CLP-INDUCED SEPSIS

PMN depletion 12hr after onset of sepsis (CLP)

a. Improves survival
b. Reduces blood CFUs
c. Reduces evidence of liver and renal dysfunction
d. Reduces levels of serum cytokines after CLP/.

Accordingly, such evidence indicates that PMNs contribute to organ dysfuntion, lethality and the cytokine storm" after CLP.

HARMFUL EFFECTS OF COMPLEMENT IN SEPSIS



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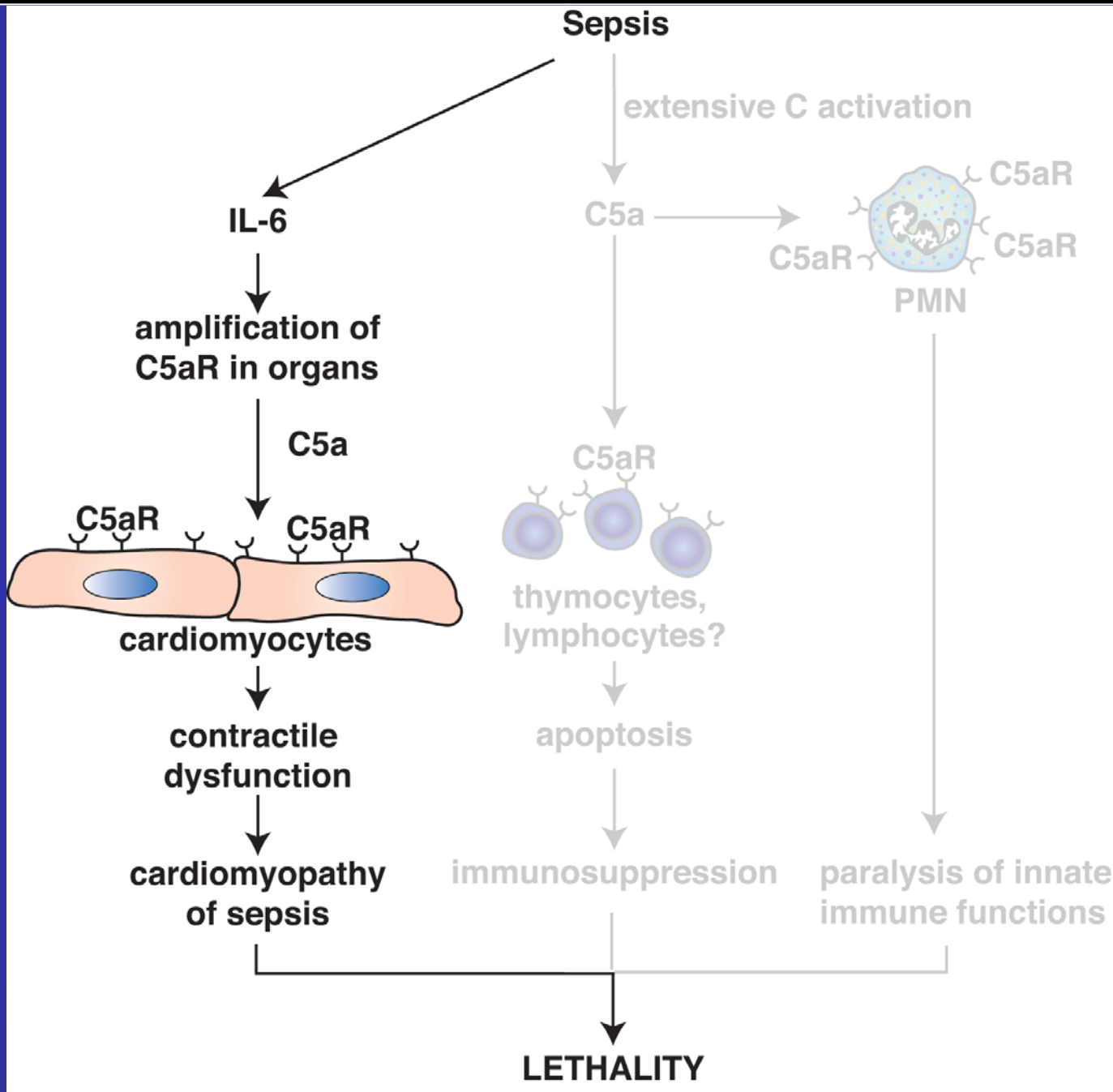

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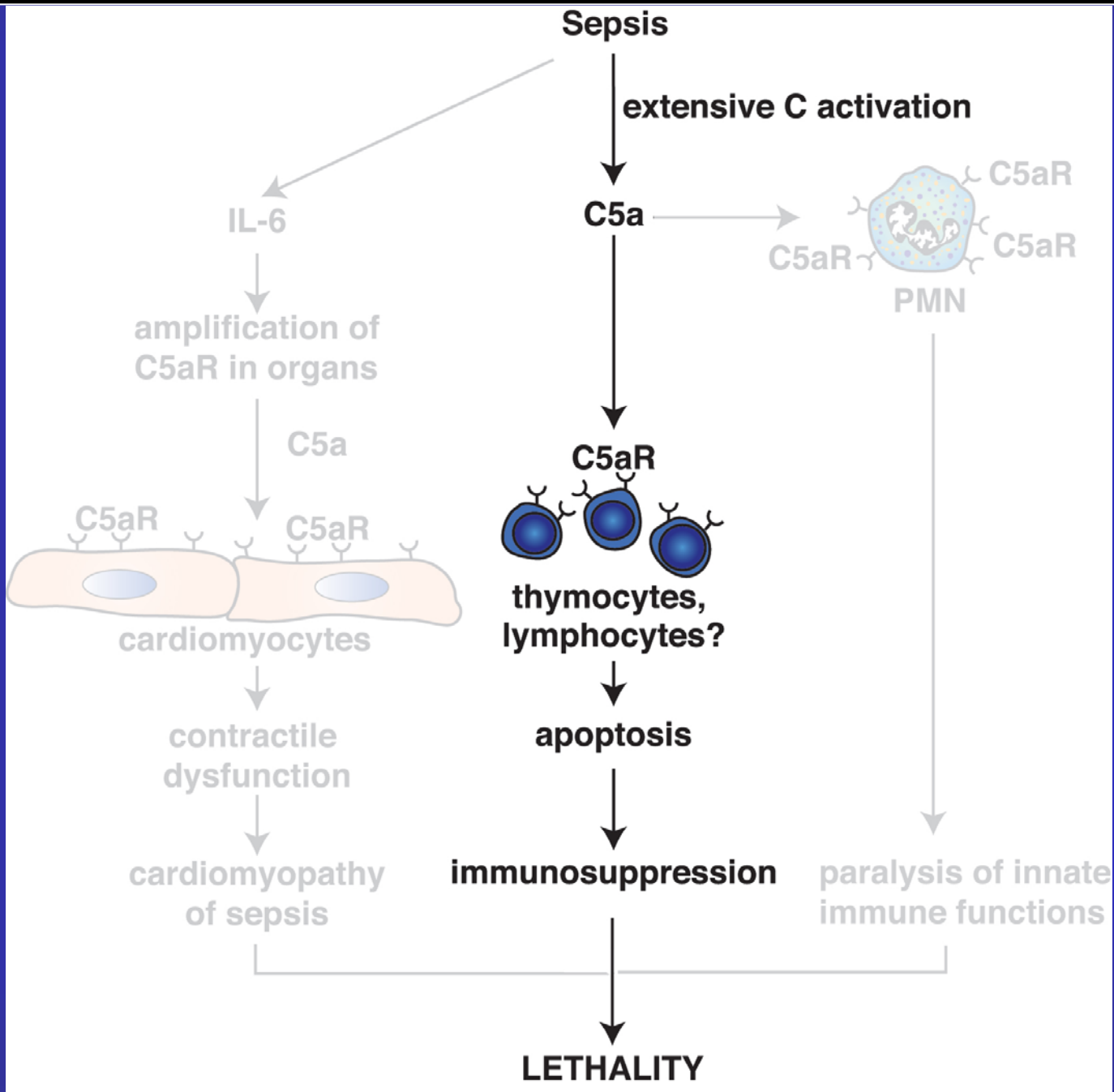

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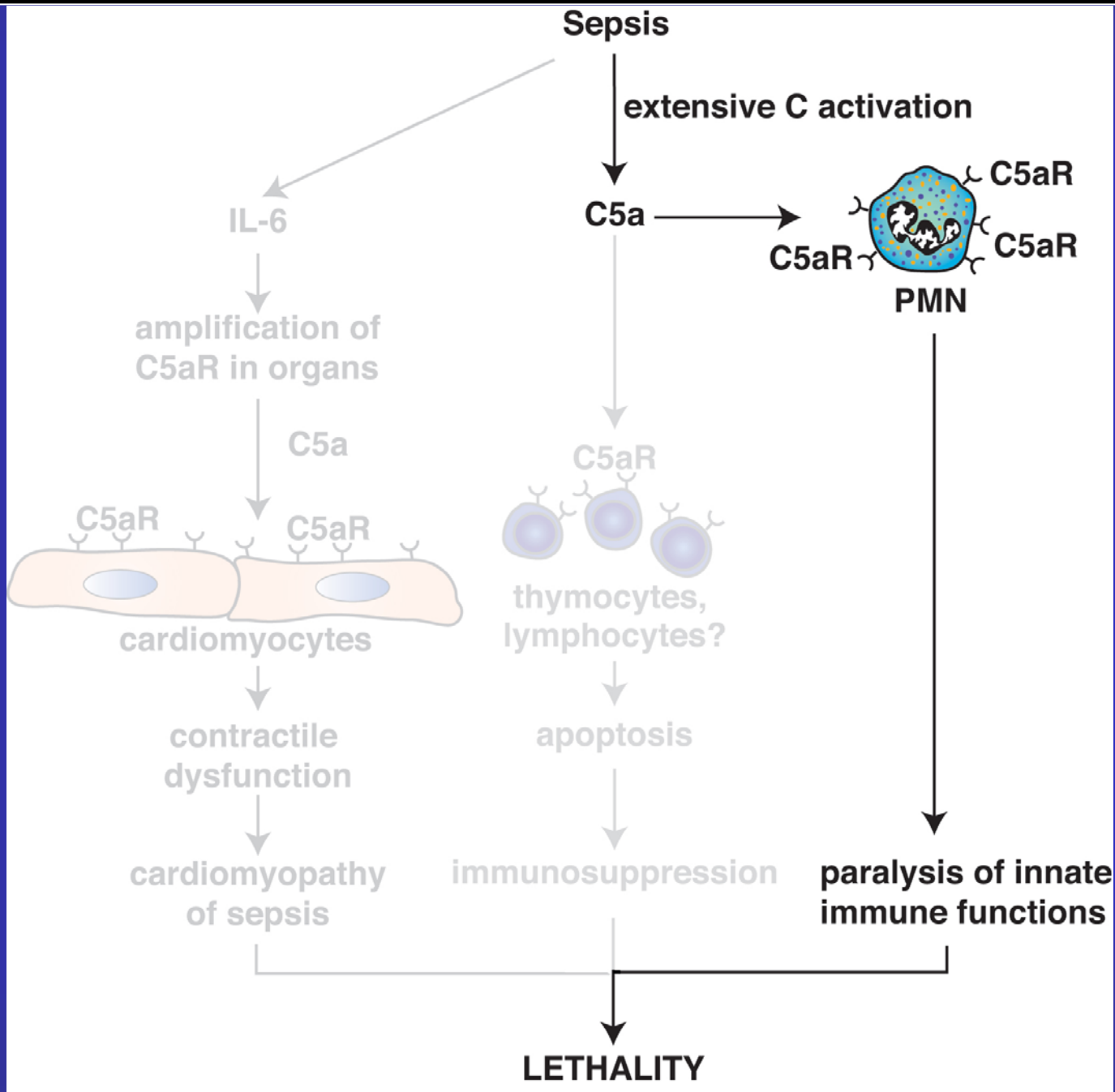

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